Atomic Description of Alzheimer's Amyloid Beta Oligomers

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Cells have elaborate procedures to ensure that proteins fold correctly. In the event that a protein misfolds, cellular mechanisms are in place to detect and degrade it before it can become toxic. Despite these efforts, a range of debilitating human diseases is associated with protein misfolding. Lately, most attention has been paid to a group of diseases where proteins or peptides convert from their normally soluble forms to aggregates of insoluble fibrils or plaques. The final forms of these aggregates often have an ordered assembly of cross β-sheet fibrils and are referred to as amyloids. The deposits of amyloid are associated with at least 20 diseases, including such diverse entities as Alzheimer's disease (amyloid beta), prion diseases (prion), familial polyneuropathy (transthyretin), type 2 diabetes mellitus (islet amyloid or amylin), systemic amyloidosis (lysozyme or transthyretin), Parkinson's disease (a-synuclein), and Huntington's disease (huntingtin). The fact that many of the ordinary proteins can form amyloid fibrils under conditions that bias the population of unfolded conformations makes the study of fibril formation very intriguing.

All-atom simulations have been carried out on monomer and dimer of the aggregation-prone fragment (16-22) of amyloid beta peptide ($A\beta_{16-22}$), which is implicated in Alzheimer's disease (Fig. 1). It is motivated by the recent clinical studies that have suggested oligomers as the possible pathological agents. A thorough understanding of dimer formation provides a detailed picture of forces that drive the interaction between fragments. The theoretical challenge is to capture the relevant configurational ensembles of the $A\beta_{16-22}$ dimers at the atomic level as a function of temperature (T) in explicit aqueous solution. The replica exchange molecular dynamics method, which has been successfully applied to peptide folding, is used as a means of sampling the configurational space with proper Boltzmann weighting so that the structural, motional, and thermodynamic description of self-assembly can be obtained.

The free-energy landscape showing the delicate balance between different monomer and dimer conformations is mapped along carefully chosen reaction coordinates (Fig. 2). The canonical ensembles at 38 different T are used to describe the thermodynamics and the relative stabilities of at least six different dimer conformations, including parallel and antiparallel orientations. In summary, this all-atom simulation study reveals that dimers of the aggregation-prone fragment of Aβ peptide do not necessarily adopt only the parallel and antiparallel conformations commonly seen in the amyloid fibril. Six highly populated conformations are found, with the parallel conformation preferred at lower T, and the antiparallel conformation is preferred at higher T (Fig. 3). Furthermore, we delineate the nature of the molecular forces that activate and stabilize these different dimer conformations as a function of T, especially as related to the secondary structural propensity of the monomer [1]. This study also identified parallel loop dimer conformations that are stabilized due to specific interactions with water molecules. Currently, aggregation of a large number of fragments of the same peptide is under consideration (Fig. 4). Calculations were carried out on Pink as part of the Institutional Computing Program.

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[1] S. Gnanakaran et al., *J Am Chem Soc*, **128**, 2158 (2006).

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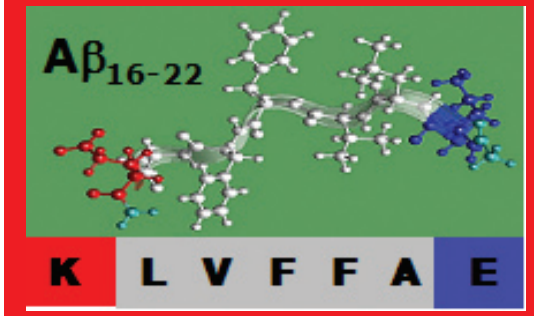

Fig. 1. Aggregation prone segment of amyloid beta peptide.

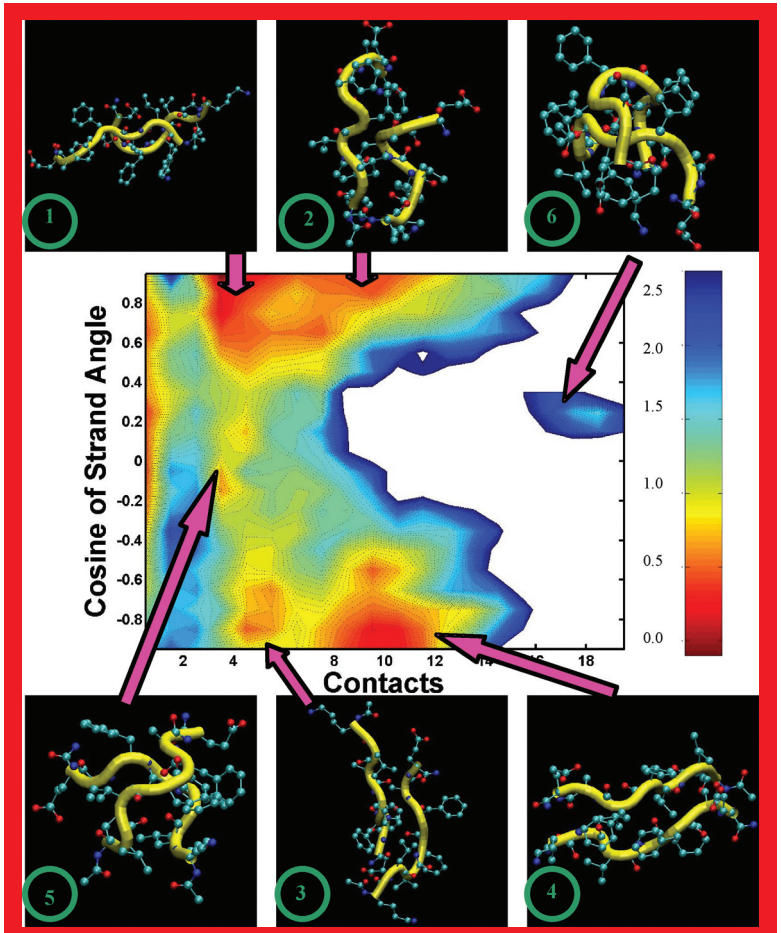

Fig. 2. Free energy landscape of $A\beta_{16\text{-}22}$ dimers at 310K. Representative conformations of dimers are shown.

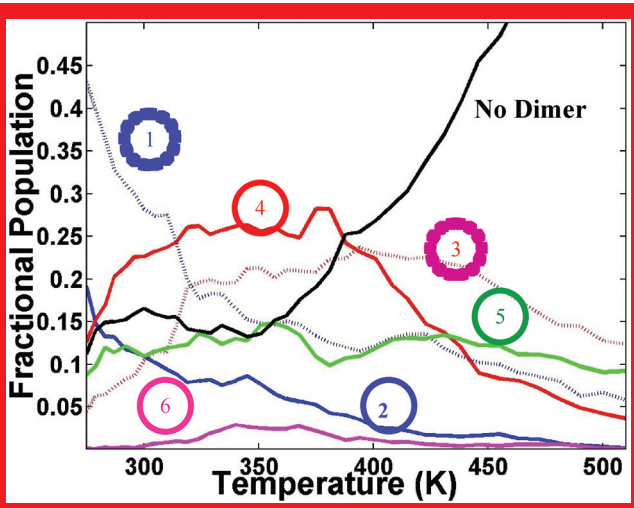

Fig. 3. Temperature profile of dimers identified in Fig. 2.

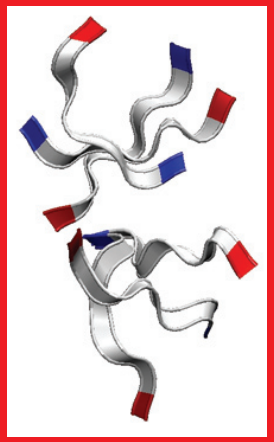

Fig. 4. Snapshot from simulations of six peptide fragments.